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(57) Abstract

There is provided a contrast medium composition comprising a physiologically tolerable manganese compound, an uptake promoter and a physiologically tolerable carrier or excipient, having a manganese concentration of at least 0.3mM or being in a dosage unit form containing at least 300 μmol manganese, wherein the uptake promoter comprises a physiologically tolerable reducing compound containing an α-hydroxy ketone group, a physiologically tolerable acid containing α- and/or β-hydroxy or amino groups, or a salt thereof, and/or vitamin D. Such compositions are particularly suitable for imaging of the liver.

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COMPOSITIONS

The present invention relates to improvements in and relating to magnetic resonance imaging (MRI) and in particular to compositions for use as or in the preparation of MRI contrast media for imaging of the stomach, intestine, liver, bile duct and gall bladder.

MRI is now well established as a medical diagnostic tool. The ability of the technique to generate high quality images and to differentiate between soft tissues without requiring the patient to be exposed to ionizing radiation has contributed to this success.

Although MRI can be performed without using added contrast media, it has been found that substances which affect the nuclear spin reequilibration of the nuclei (hereinafter the "imaging nuclei" - generally water protons in body fluids and tissues) responsible for the magnetic resonance (MR) signals from which the images are generated may be used to enhance image contrast and, accordingly, in recent years, many such materials have been suggested as MRI contrast agents.

The enhanced contrast obtained with the use of contrast agents enables particular organs or tissues to be visualized more clearly by increasing or by decreasing the signal level of the particular organ or tissue relative to that of its surroundings. Contrast agents raising the signal level of the target site relative to that of its surroundings are termed "positive" contrast agents whilst those lowering the signal level relative to surroundings are termed "negative" contrast agents.

The majority of materials now being proposed as MRI contrast media achieve a contrast effect because they contain paramagnetic, superparamagnetic or ferromagnetic species.

For ferromagnetic and superparamagnetic contrast agents, which are negative MRI contrast agents, the enhanced image contrast derives primarily from the reduction in the spin reequilibration parameter known as T_2 or as the spin-spin relaxation time, a reduction arising from the effect on the imaging nuclei of the fields generated by the ferromagnetic or superparamagnetic particles.

Paramagnetic contrast agents on the other hand may be either positive or negative MRI contrast agents. The effect of paramagnetic substances on magnetic resonance signal intensities is dependent on many factors, the most important of which are the concentration of the paramagnetic substance at the imaged site, the nature of the paramagnetic substance itself and the pulse sequence and magnetic field strength used in the imaging routine. Generally, however, paramagnetic contrast agents are positive MRI contrast agents at low concentrations where their T_1 lowering effect dominates and negative MRI contrast agents at higher concentrations where their T_2 lowering effect is dominant. In either event, the relaxation time reduction results from the effect on the imaging nuclei of the magnetic fields generated by the paramagnetic centres.

The use of paramagnetic, ferromagnetic and superparamagnetic materials as MRI contrast agents has been widely advocated and broad ranges of suitable materials have been suggested in the literature.

An example of a physiologically tolerable paramagnetic material known for use as an MRI contrast agent is manganese ion, which may conveniently be used in the form of its salts or chelates. Indeed, even at very low i.v. dosages (about 5-10 μmol/kg bodyweight) manganese has been found to be particularly effective as a contrast agent for imaging of the liver.

However manganese, when administered intravenously as a contrast agent, may be teratogenic at clinical

dosages. Administered intravenously, manganese is also known to interfere with the normal functioning of the heart by replacement of calcium in the calcium pump of the heart.

In order to reduce the direct effect on the heart, oral administration has been proposed. This ensures passage of the contrast agent through the liver before going to the heart.

Oral administration of $MnCl_2$ as a liver imaging MR contrast agent has been proposed and orally administered $MnCl_2$ has not been found to be teratogenic. However, the absorption of $MnCl_2$ through the gut is poor, and as a result the dosage required for clinical efficacy is of the order of 100-1000 μmol/kg bodyweight. In the event of damage to the gut resulting in increased uptake, such a high dosage level still has the potential for causing undesired adverse effects, eg. cardiac effects.

We have now surprisingly found that gastrointestinal tract manganese contrast agents suitable for imaging of the liver may be produced by the incorporation of an uptake promoter capable of enhancing manganese transport across the membranes of the g.i. tract.

Compounds which have been found to be suitable for use as uptake promoters include reducing compounds containing an α-hydroxy ketone group (-C(OH)-CO-), acids containing α- and/or β-hydroxy or amino groups, as well as vitamin D.

Thus, viewed from one aspect the present invention provides a contrast medium composition comprising a physiologically tolerable manganese compound, an uptake promoter and a physiologically tolerable carrier or excipient, having a manganese concentration of at least 0.3mM or being in a dosage unit form containing at least 300 μmol manganese, wherein the uptake promoter comprises a physiologically tolerable reducing compound containing an α-hydroxy ketone group, a physiologically

tolerable acid containing α- and/or β-hydroxy or amino groups, or a salt thereof, and/or vitamin D.

As used herein, the expression "acid containing α- and/or β-hydroxy or amino groups" is intended to include aromatic acids containing ortho-hydroxy or ortho-amino groups.

The contrast medium composition according to the invention may comprise a manganese compound together with a mixture of several uptake promoters.

The manganese compound, which preferably is soluble in gastrointestinal fluid may for example be a chelate or a salt, or may be a mixture of different salts and/or chelates. Particularly preferred are metal chelates and salts in which the manganese is present as Mn(II) rather than Mn(III) since the former has a higher magnetic moment and thus is more effective as an MR contrast agent.

The reducing nature of the uptake promoter is important since normal uptake of manganese by the gut tends to favour Mn(II) rather than Mn(III).

Preferred compositions according to the invention are those in which the reducing compound further contains an oxygen atom in a heterocyclic ring structure.

Particularly preferred as an uptake promoter in the compositions of the invention is ascorbic acid which has been found to increase the uptake of manganese in the liver about 5-fold compared with oral administration of $MnCl_2$ alone. This surprising increase is demonstrated in Figure 2 of the accompanying drawings. Moreover ascorbic acid (vitamin C) is particularly preferred as an uptake promoter since it is cheap, readily available and particularly well tolerated by the body.

Yet more particularly preferred compositions in accordance with the invention are those in which the uptake promoter is kojic acid. The dramatic increase in the uptake of manganese in the liver following

administration of $MnCl_2$ + kojic acid can be seen from Figure 5 of the accompanying drawings.

Examples of acids which have been found to be particularly effective as uptake promoters in the compositions of the invention include carboxylic acids, e.g. gluconic and salicyclic acid. The effect of the addition of salicylic acid to $MnCl_2$ on MRI enhancement of the liver can be seen in Figure 8 of the accompanying drawings. α- and β- amino acids have also been found to be useful as uptake promoters, in particular α-amino acids, e.g. glycine, valine, glutamine, aspartic acid, glutamic acid, lysine, arginine, cysteine and methionine, especially arginine, lysine and aspartic acid. The effect of addition of various α-amino acids to $MnCl_2$ on MRI enhancement of the liver is shown in accompanying Figure 9.

Other preferred compositions in accordance with the invention are those which comprise vitamin D as an uptake promoter.

Using the compositions of the invention, the liver can be effectively MR imaged with a significant reduction in the dosage of manganese otherwise required. Thus, for example, a 50% enhancement of the liver can be obtained by oral administration of 100 μmol manganese/kg body weight and 1 mmol ascorbic acid/kg. Such a dosage results in the same degree of enhancement of the liver as 5 μmol Mn(II)/kg body weight ($MnCl_2$, i.v.) or as 500 μmol Mn(II)/kg body weight ($MnCl_2$, p.o.).

Figure 1 hereto demonstrates the effect of p.o. administration of $MnCl_2$ and ascorbic acid on MR liver enhancement compared with p.o. administration of $MnCl_2$ alone.

Increase in the ratio of ascorbic acid to $MnCl_2$ results in an increase in the enhancement effect obtained. This dose-response relationship can be seen from Figure 2 hereto.

The gradual increase in enhancement of the liver

with time following administration of a composition in accordance with the invention enables the dynamics of uptake of the contrast agent by the liver to be monitored (see for example Figure 2). This is of particular importance in enabling identification of areas of healthy tissue and areas of possible tumor growth.

In the compositions according to the invention, the preferred molar ratio of manganese to uptake promoter is from 1:0.2 to 1:50, eg. 1:1 to 1:20, especially 1:3 to 1:6, particular preferably about 1:5.

The uptake promoter may if desired be present in whole or in part as the counterion to the manganese ions. Thus in one embodiment the composition of the invention comprises as both manganese compound and uptake promoter a manganese salt of a reducing compound containing an α-hydroxy ketone group or a manganese salt of an acid containing α- and/or β- hydroxy or amino groups, eg. manganese (II) ascorbate or manganese salicylate.

The compositions according to the invention may be used to achieve a so-called "double contrast effect" by increasing the signal level from the liver whilst at the same time decreasing that from the surrounding tissues, in particular from the gut. Such an effect enables yet further enhancement of the liver.

A double contrast effect and margin definition can be achieved with the compositions of the invention since the resulting manganese ion concentration within the g.i. tract will generally be such as to create a signal suppressing effect there. In this case, to avoid image artefacts resulting from pockets of the gut being contrast agent free, it is desirable to incorporate in the compositions a viscosity enhancing agent and desirably also an osmoactive agent. Examples of suitable viscosity enhancers and osmoactive agents are described in WO 91/01147 and WO 91/01148.

In a particularly preferred embodiment, the compositions of the invention may be used in combination with a second contrast agent having either a positive or negative contrast effect. Preferably the compositions of the invention are used in combination with a second contrast agent having an opposing contrast effect. This results in a "double contrast effect" enabling visualisation and margin definition of the liver to be particularly enhanced.

As mentioned above, paramagnetic materials such as manganese ions may act as either positive or negative MRI contrast agents depending upon a number of factors, including the concentration of the ions at the imaging site and the magnetic field strength used in the imaging procedure. At the concentrations of manganese contemplated for use in the compositions of the invention, the manganese-containing contrast agent will, in general, function as a positive contrast agent. The second contrast agent is therefore conveniently a negative contrast agent and may be any negative MRI contrast agent suitable for oral administration. However, as indicated above, any MR contrast agent, negative or positive, may be used.

Examples of negative MRI contrast agents for use in combination with the compositions of the invention include known ferromagnetic and superparamagnetic species, such as for example magnetic iron oxide particles either free or enclosed within or bound to a non-magnetic matrix material such as a polysaccharide eg. LUMIREM and sulphonated polystyrene eg. ABDOSCAN®.

Further examples of contrast agents for use in combination with the compositions of the invention include Gd and Dy ions bound to a polymeric matrix, for example LUMIREM or GADOLITE (Gadolinium alumina silicate oral suspension).

When using the compositions of the invention to achieve a double contrast effect, it is particularly

preferable to incorporate a viscosity enhancing agent which attains its full viscosity enhancing effect only after administration of the contrast medium. The contrast medium is thus able to be ingested in a relatively tolerable form while yet developing the desired viscosity at or during passage towards the site which is to be imaged.

The compositions of the invention are particularly suited to use, if required after dispersion in aqueous media, for imaging of the liver. For such a purpose the compositions may be administered into the gastrointestinal tract orally, rectally or via a stomach tube.

Thus, viewed from a further aspect the present invention provides a method of generating a magnetic resonance image of a human or non-human, preferably mammalian, animal body which method comprises administering into the gastrointestinal tract of a said body a contrast medium comprising a physiologically tolerable manganese compound and a physiologically tolerable reducing compound containing an α-hydroxy ketone group or a physiologically tolerable acid containing α- and/or β- hydroxy or amino groups, or a salt thereof, and/or vitamin D, and generating a magnetic resonance image of the liver and the gastro-intestinal tract of said body.

Viewed from a yet further aspect the invention also provides a method of generating a magnetic resonance image of a human or non-human animal body, which method comprises administering into the gastrointestinal tract of a said body an effective amount of a composition comprising: (a) a first contrast agent comprising a physiologically tolerable manganese compound, a physiologically tolerable reducing compound containing an α-hydroxy ketone group or a physiologically tolerable acid containing α- and/or β- hydroxy or amino groups, or a salt thereof, and/or vitamin D, preferably having a

manganese concentration of at least 0.3mM or being in a dosage unit form containing at least 300 μmol manganese, together with (b) a second contrast agent and generating a magnetic resonance image of the liver and abdomen of said body.

It is possible to formulate the contrast medium immediately or shortly prior to administration by mixing the uptake promoter with the manganese species. Thus, in a further aspect the invention also provides an MRI contrast agent kit comprising in a first container a physiologically tolerable manganese compound, and in a second container a physiologically tolerable reducing compound containing an α-hydroxy ketone group or a physiologically tolerable acid containing α- and/or β-hydroxy or amino groups, or a salt thereof, and/or vitamin D.

Viewed from a further aspect the invention also provides an MRI contrast agent kit comprising in a first container a first contrast agent comprising a physiologically tolerable manganese compound, a physiologically tolerable reducing compound containing an α-hydroxy ketone group or a physiologically tolerable acid containing α- and/or β- hydroxy or amino groups, or a salt thereof, and/or vitamin D, preferably having a manganese concentration of at least 0.3mM or being in a dosage unit form containing at least 300 μmol manganese, and in a second container a second contrast agent comprising a particulate ferromagnetic or superparamagnetic material or Gd or Dy ions bound to a polymeric matrix.

The contrast agent compositions of the invention may of course include components other than the uptake promoter, the manganese compound, the viscosity enhancing and osmoactive agents, for example conventional pharmaceutical formulation aids such as wetting agents, buffers, disintegrants, binders, fillers, flavouring agents and liquid carrier media such

as sterile water, water/ethanol etc.

For oral administration, the pH of the composition is preferably in the acid range, eg. 2 to 7 and while the uptake promoter may itself serve to yield a composition with this pH, buffers or pH adjusting agents may be used.

The contrast media may be formulated in conventional pharmaceutical administration forms, such as tablets, capsules, powders, solutions, dispersions, syrups, suppositories etc.

The preferred dosage of the composition according to the present invention will vary according to a number of factors, such as the administration route, the age, weight and species of the subject and the particular uptake promoter used. Conveniently, the dosage of manganese will be in the range of from 5 to 500 μmol/kg bodyweight, preferably from 5 to 150 μmol/kg bodyweight, more preferably from 10 to 100 μmol/kg bodyweight, while the dosage of the uptake promoter will be in the range of from 5 μmol to 1 mmol/kg bodyweight, preferably from 25 μmol to 0.5 mmol/kg bodyweight.

Preferred embodiments of the invention will now be described by reference to the following non-limiting Examples and the accompanying drawings, in which:

Figure 1 is a graph illustrating the effect of p.o. administration of different Mn^{2+} salts on liver enhancement;

Figure 2 is a graph illustrating the effect of p.o. administration of $MnCl_2$ + ascorbic acid on liver enhancement at varying concentrations of ascorbic acid; and

Figure 3 is a graph illustrating the effect of p.o. administration of different doses of $MnCl_2$ containing 0.1 mmol/kg ascorbic acid on liver enhancement.

Figure 4 is a graph illustrating the effect of the addition of ascorbic acid or ascorbic acid-palmitate to $MnCl_2$ on enhancement of the liver.

Figure 5 is a graph illustrating the effect of the addition of ascorbic acid or kojic acid to $MnCl_2$ on enhancement of the liver.

Figure 6 is a graph illustrating the results of a pharmacokinetic study to determine the variation in concentration of Mn(II) in the blood following administration of various Mn(II)-containing compositions.

Figure 7 is a graph comparing the effect on liver enhancement of i.v. administration of Mn DPDP (S-095) with that of p.o. administration of $MnCl_2$ + ascorbic acid.

Figure 8 is a graph illustrating the effect of the addition of ascorbic and salicylic acids to $MnCl_2$ on liver enhancement.

Figure 9 is a graph illustrating the effect of the addition of different amino acids to $MnCl_2$ on liver enhancement.

Figure 10 illustrates transversal T1-weighted (SE 57/13; 2.4 T) liver images from a control rat and from three rats 2 hours after oral administration of 200 μmol/kg $MnCl_2$ + 1000 μmol/kg ascorbate. The signal intensity of the liver is substantially increased after gavage administration of Mn^{2+} and ascorbate.

Figure 11 illustrates coronal T1-weighted (SE 90/17; 2.4 T) liver images from two rats 2 hours after oral administration of 200 μmol/kg $MnCl_2$ + 1000 μmol/kg ascorbate. The signal intensity in the gastrointestinal lumen is reduced after administration of Mn^{2+}.

Figures 12 and 13 are graphs illustrating the effect of the addition of ABDOSCAN® to Mn-ascorbate on the enhancement of the liver.

Figure 14 illustrates transversal T1-weighted (SE 57/13; 2.4 T) liver images from a control rat and from three rats 2 hours after oral administration of 200 μmol/kg $MnCl_2$ + 1000 μmol/kg ascorbate + ABDOSCAN® (21

μmol/kg Fe). The addition of ABDOSCAN did not influence the signal intensity of the liver.

Figure 15 illustrates coronal T1-weighted (SE 90/17; 2.4 T) liver images from a control rat and from a rat 2 hours after oral administration of 200 μmol/kg $MnCl_2$ + 1000 μmol/kg ascorbate + ABDOSCAN® (21 μmol/kg Fe). The signal intensity in the gastrointestinal lumen is markedly reduced after co-administration of Mn^{2+} and ABDOSCAN.

For the measurement of the curves of Figures 1 to 9 the following materials were used:

<u>Figure 1</u>

<u>Mn-ascorbate</u>

$MnCl_2 \times 2H_2O$		6.48	g
Ascorbic acid		35.2	g
Water	<u>ad</u>	1000	ml

<u>Mn-gluconate</u>

Mn-gluconate		19.2	g
Water	<u>ad</u>	1000	ml

<u>Mn-citrate</u>

$MnCl_2 \times 2H_2O$		6.48	g
Na_3-citrate x $2H_2O$		23.5	g
Water	<u>ad</u>	1000	ml

<u>Figure 2</u>

<u>$MnCl_2$</u>

$MnCl_2 \times 2H_2O$		6.48	g
Water	<u>ad</u>	1000	ml

<u>$MnCl_2$ + 0.1 mmol/kg ascorbic acid</u>

$MnCl_2 \times 2H_2O$		6.48	g
Ascorbic acid		3.52	g

Water	ad	1000 ml

$MnCl_2$ + 0.4 mmol/kg ascorbic acid

$MnCl_2 \times 2H_2O$		6.48 g
Ascorbic acid		14.1 g
Water	ad	1000 ml

$MnCl_2$ + 1.0 mmol/kg ascorbic acid

$MnCl_2 \times 2H_2O$		6.48 g
Ascorbic acid		35.2 g
Water	ad	1000 ml

Figure 3

$MnCl_2$ (0.2 mmol/kg) + ascorbic acid

$MnCl_2 \times 2H_2O$		6.48 g
Ascorbic acid		3.52 g
Water	ad	1000 ml

$MnCl_2$ (0.5 mmol/kg) + ascorbic acid

$MnCl_2 \times 2H_2O$		16.2 g
Ascorbic acid		3.52 g
Water	ad	1000 ml

$MnCl_2$ (2.0 mmol/kg) + ascorbic acid

$MnCl_2 \times 2H_2O$		64.8 g
Ascorbic acid		3.52 g
Water	ad	1000 ml

Figure 4

$MnCl_2$

$MnCl_2 \times 2H_2O$		13.0 g
Water	ad	1000 ml

$MnCl_2$ + ascorbic acid - palmitate (0.4 mmol/kg)

L-ascorbic acid 6-palmitate		66.4 g

Polyethylene glycol 300	ad	1000	ml

Figure 5

$MnCl_2$ + kojic acid (0.4 mmol/kg)

$MnCl_2 \times 2H_2O$		6.48	g
Kojic acid		11.4	g
Water	ad	1000	ml

Figure 8

$MnCl_2$ (0.2 mmol/kg)

$MnCl_2 \times 2H_2O$		6.48	g
Water	ad	1000	ml

$MnCl_2$ (0.2 mmol/kg) + ascorbic acid (0.4 mmol/kg)

$MnCl_2 \times 2H_2O$		6.48	g
Ascorbic acid		14.1	g
Water	ad	1000	ml

$MnCl_2$ (0.2 mmol/kg) + salicylic acid (0.4 mmol/kg)

$MnCl_2 \times 2H_2O$		6.48	g
Salicyclic acid sodium salt		12.8	g
Water	ad	1000	ml

Figure 9

$MnCl_2$ (0.2 mmol/kg)

$MnCl_2 \times 2H_2O$		6.48	g
Water	ad	1000	ml

$MnCl_2$ (0.2 mmol/kg) + ascorbic acid (0.4 mmol/kg)

$MnCl_2 \times 2H_2O$		6.48	g
Ascorbic acid		14.1	g
Water	ad	1000	ml

<u>$MnCl_2$ (0.2 mmol/kg) + glycine (0.4 mmol/kg)</u>

$MnCl_2 \times 2H_2O$		6.48	g
Glycine		7.76	g
Water	<u>ad</u>	1000	ml

<u>$MnCl_2$ (0.2 mmol/kg) + valine (0.4 mmol/kg)</u>

$MnCl_2 \times 2H_2O$		6.48	g
Valine		9.36	g
Water	<u>ad</u>	1000	ml

<u>$MnCl_2$ (0.2 mmol/kg) + glutamine (0.4 mmol/kg)</u>

$MnCl_2 \times 2H_2O$		6.48	g
Glutamine		11.7	g
Water	<u>ad</u>	1000	ml

<u>$MnCl_2$ (0.2 mmol/kg) + aspartic acid (0.4 mmol/kg)</u>

$MnCl_2 \times 2H_2O$		6.48	g
Aspartic acid		13.8	g
Water	<u>ad</u>	1000	ml

<u>$MnCl_2$ (0.2 mmol/kg) + glutamic acid (0.4 mmol/kg)</u>

$MnCl_2 \times 2H_2O$		6.48	g
Glutamic acid monosodium salt monohydrate		15.0	g
Water	<u>ad</u>	1000	ml

<u>$MnCl_2$ (0.2 mmol/kg) + lysine (0.4 mmol/kg)</u>

$MnCl_2 \times 2H_2O$		6.48	g
Lysine monohydrochloride		14.6	g
Water	<u>ad</u>	1000	ml

<u>$MnCl_2$ (0.2 mmol/kg) + arginine (0.4 mmol/kg)</u>

$MnCl_2 \times 2H_2O$		6.48	g
Arginine monohydrochloride		16.9	g
Water	<u>ad</u>	1000	ml

$MnCl_2$ (0.2 mmol/kg) + cysteine (0.4 mmol/kg)

$MnCl_2 \times 2H_2O$		6.48 g
Cysteine monohydrochloride monohydrate		14.0 g
Water	ad	1000 ml

$MnCl_2$ (0.2 mmol/kg) + methionine (0.4 mmol/kg)

$MnCl_2 \times 2H_2O$		6.48 g
Methionine		11.9 g
Water	ad	1000 ml

For the measurement of the curves of Figures 12 and 13 the following materials were used:

$MnCl_2 \times 2H_2O$		0.567 g
Ascorbic acid		3.08 g
ABDOSCAN®		23.4 mg Fe (one dose-package)
Water	ad	200 ml

Example 1

Oral Composition

$MnCl_2 \times 2H_2O$		6.48 g
Ascorbic acid		35.2 g
Water	ad	1000 ml

The manganese chloride and ascorbic acid are dissolved in sterile deionised water. The dose for a 70 kg adult human would be 350 ml, taken orally.

Example 2

Oral Composition

$MnCl_2 \times 2H_2O$		6.48 g
Kojic acid		11.4 g

Water	ad	1000	ml

The manganese chloride and kojic acid are dissolved in sterile deionised water. The dose for a 70 kg adult human would be 350 ml, taken orally.

Example 3

Oral Composition

A.

$MnCl_2 \times 2H_2O$		13.0	g
Water	ad	1000	ml

B.

L-ascorbic acid 6-palmitate		66.4	g
Polyethylene glycol 300	ad	1000	ml

The dose for a 70 kg adult human would be 175 ml of A and 175 ml of B, taken orally.

Example 4

Oral Composition

$MnCl_2 \times 2H_2O$		0.567	g
Ascorbic acid		3.08	g
ABDOSCAN®		23.4	mg Fe
Water	ad	200	ml

The dose for a 70 kg adult human would be 4 x 200 ml, taken orally.

Example 5

Oral Composition - $MnCl_2$ (0.2 mmol/kg) + vitamin D (0.4 mmol/kg)

A.

$MnCl_2 \times 2H_2O$		13.0	g
Water	ad	1000	ml

B.

Vitamin D		30.0	g
Polyethylene glycol 300	ad	1000	ml

Claims

1. A contrast medium composition comprising a physiologically tolerable manganese compound, an uptake promoter and a physiologically tolerable carrier or excipient, having a manganese concentration of at least 0.3mM or being in a dosage unit form containing at least 300 μmol manganese, wherein the uptake promoter comprises a physiologically tolerable reducing compound containing an α-hydroxy ketone group, a physiologically tolerable acid containing α- and/or β-hydroxy or amino groups, or a salt thereof, and/or vitamin D.

2. A composition as claimed in claim 1 wherein the uptake promoter comprises one or more of the compounds defined in claim 1.

3. A composition as claimed in claim 1 or claim 2 wherein the manganese compound is a chelate or a salt in which the manganese is present as Mn(II).

4. A composition as claimed in any one of claims 1 to 3 wherein the reducing compound further contains an oxygen atom in a heterocyclic ring structure.

5. A composition as claimed in any one of claims 1 to 4 wherein the uptake promoter is ascorbic acid.

6. A composition as claimed in any one of claims 1 to 4 wherein the uptake promoter is kojic acid.

7. A composition as claimed in any one of claims 1 to 3 wherein the acid is gluconic or salicylic acid.

8. A composition as claimed in any one of claims 1 to 3 wherein the acid is an α- or β-amino acid.

9. A composition as claimed in claim 8 wherein the acid is glycine, valine, glutamine, aspartic acid, glutamic acid, lysine, arginine, cysteine or methionine.

10. A composition as claimed in claim 8 or claim 9 further comprising vitamin D.

11. A composition as claimed in any one of claims 1 to 3 wherein the uptake promoter is vitamin D.

12. A composition as claimed in any preceding claim wherein the molar ratio of manganese to uptake promoter is from 1:0.2 to 1:50.

13. A composition as claimed in any preceding claim wherein the uptake promoter is present in whole or in part as the counterion to the manganese ions.

14. A method of generating a magnetic resonance image of a human or non-human animal body which method comprises administering into the gastrointestinal tract of a said body a contrast medium comprising a physiologically tolerable manganese compound and a physiologically tolerable reducing compound containing an α-hydroxy ketone group or a physiologically tolerable acid containing α- and/or β- hydroxy or amino groups, or a salt thereof, and/or vitamin D, and generating a magnetic resonance image of the liver and abdomen of said body.

15. An MRI contrast agent kit comprising in a first container a physiologically tolerable manganese compound, and in a second container a physiologically tolerable reducing compound containing an α-hydroxy ketone group, or a physiologically tolerable acid containing α- and/or β- hydroxy or amino groups, or a salt thereof, and/or vitamin D.

16. A contrast medium composition comprising:

(a) a composition as claimed in any one of claims 1 to 13, together with

(b) a second contrast agent.

17. A composition as claimed in claim 16 wherein the second contrast agent has an opposing contrast effect to said first contrast agent.

18. A composition as claimed in claim 16 or claim 17 wherein the second contrast agent has a negative contrast effect.

19. A composition as claimed in claim 16 or claim 17 wherein the second contrast agent has a positive contrast effect.

20. A composition as claimed in claim 16 or claim 17 wherein the second contrast agent comprises a particulate ferromagnetic or superparamagnetic material.

21. A composition as claimed in claim 16 or claim 17 wherein the second contrast agent comprises Gd or Dy ions bound to a polymeric matrix.

22. A method of generating a magnetic resonance image of a human or non-human animal body, which method comprises administering into the gastrointestinal tract of a said body an effective amount of a composition as defined in claim 16 and generating a magnetic resonance image of the liver and abdomen of said body.

23. An MRI contrast agent kit comprising in a first container a first contrast agent comprising a physiologically tolerable manganese compound, a physiologically tolerable reducing compound containing an α-hydroxy ketone group or a physiologically tolerable acid containing α- and/or β- hydroxy or amino groups, or

a salt thereof, and/or vitamin D, and in a second container a second contrast agent as defined in claim 20 or claim 21.

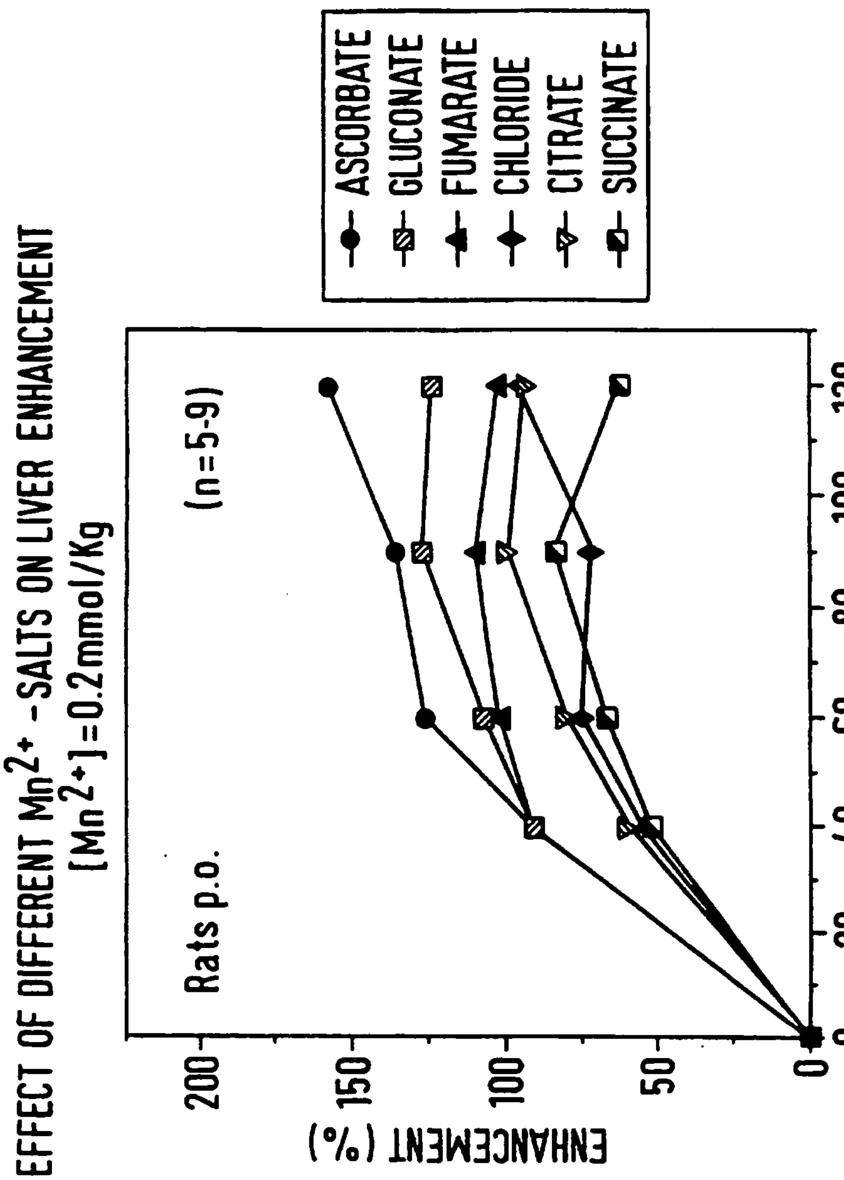

EFFECT OF DIFFERENT Mn^{2+} -SALTS ON LIVER ENHANCEMENT
$[Mn^{2+}]$=0.2mmol/Kg
Rats p.o.
(n=5-9)
ENHANCEMENT (%)
TIME (min)
0
50
100
150
200
0
20
40
60
80
100
120
ASCORBATE
GLUCONATE
FUMARATE
CHLORIDE
CITRATE
SUCCINATE

FIG. 1

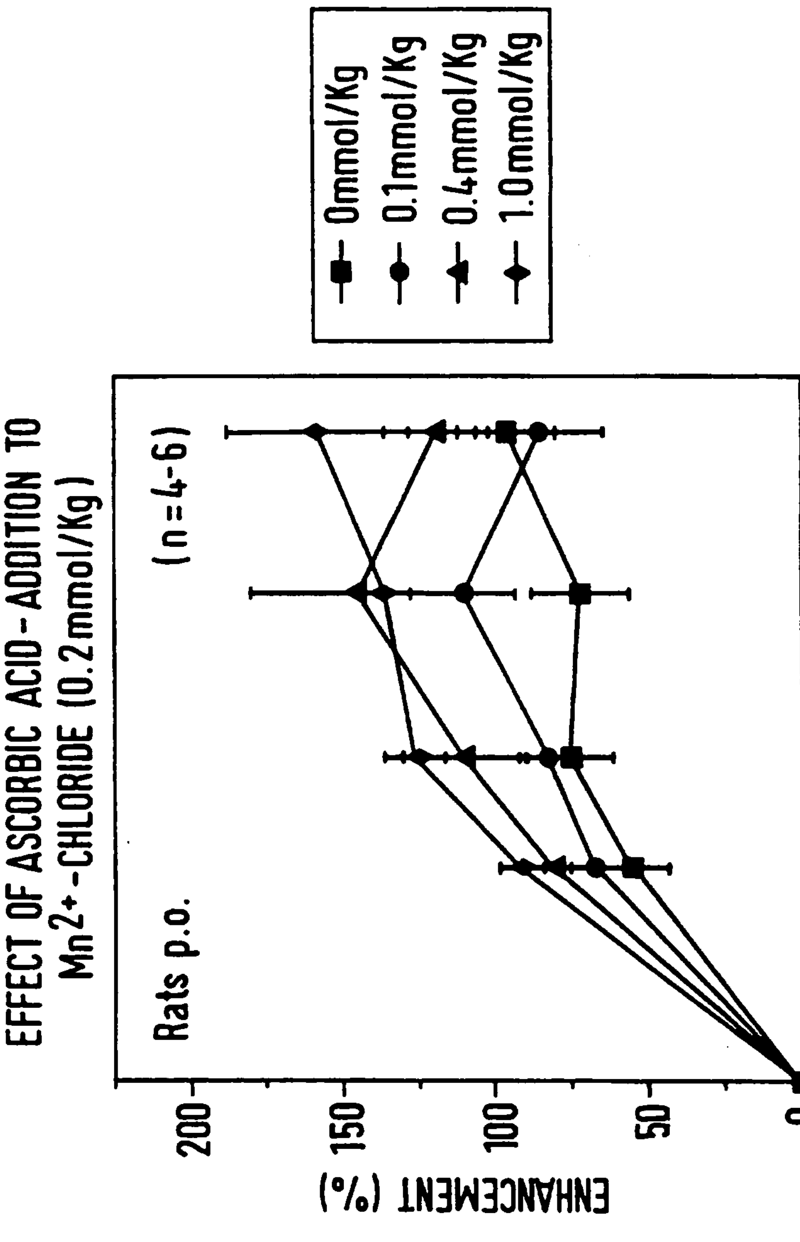
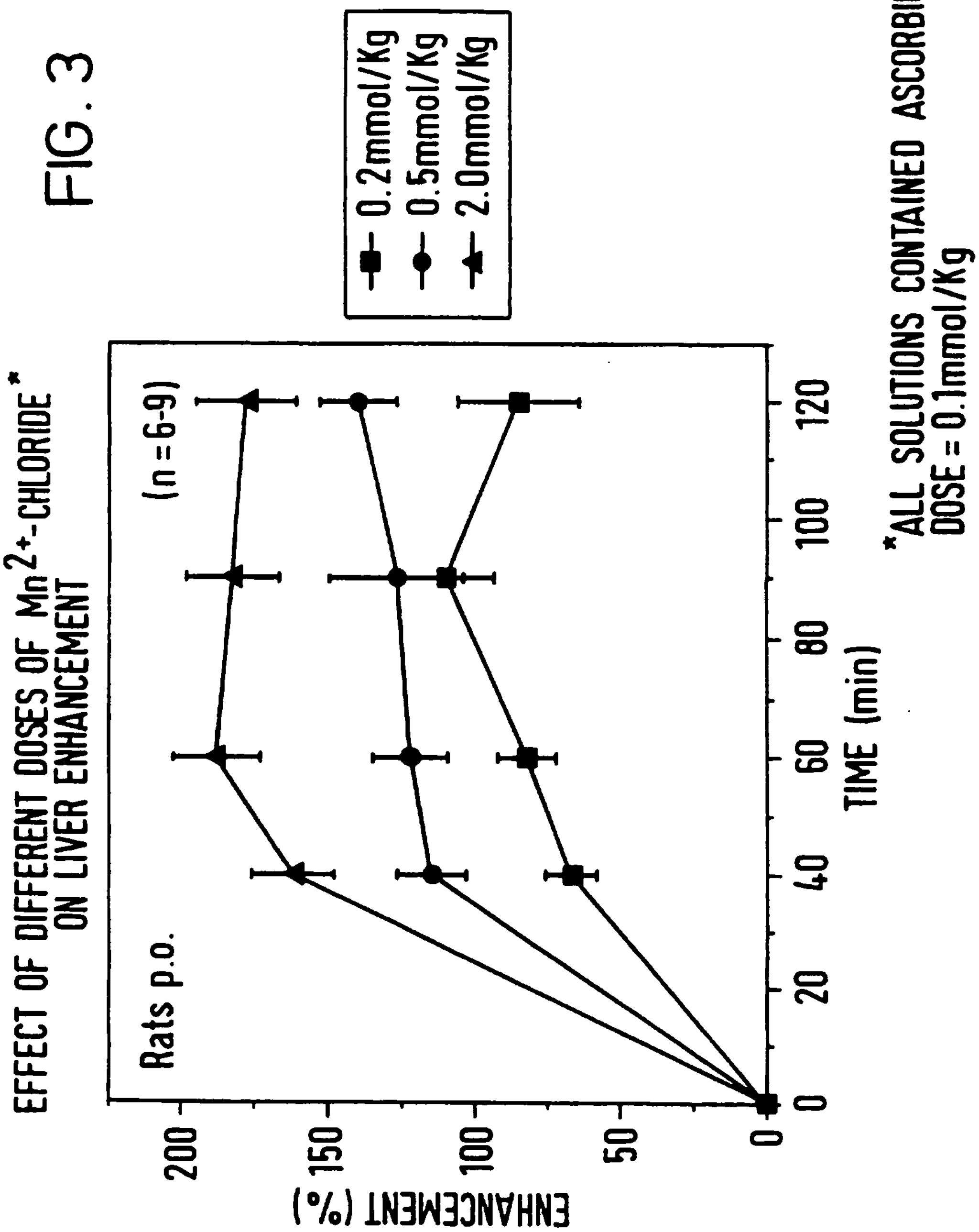

EFFECT OF ASCORBIC ACID - ADDITION TO
Mn2+ -CHLORIDE (0.2mmol/Kg)
Rats p.o.
(n=4-6)
0mmol/Kg
0.1mmol/Kg
0.4mmol/Kg
1.0mmol/Kg
ENHANCEMENT (%)
200
150
100
50
0
TIME (min)
0
20
40
60
80
100
120

FIG. 2

FIG. 3


EFFECT OF DIFFERENT DOSES OF Mn^{2+}-CHLORIDE*
ON LIVER ENHANCEMENT
Rats p.o.
(n = 6-9)
0.2mmol/Kg
0.5mmol/Kg
2.0mmol/Kg
ENHANCEMENT (%)
0
50
100
150
200
0
20
40
60
80
100
120
TIME (min)
*ALL SOLUTIONS CONTAINED ASCORBIC ACID;
DOSE = 0.1mmol/Kg

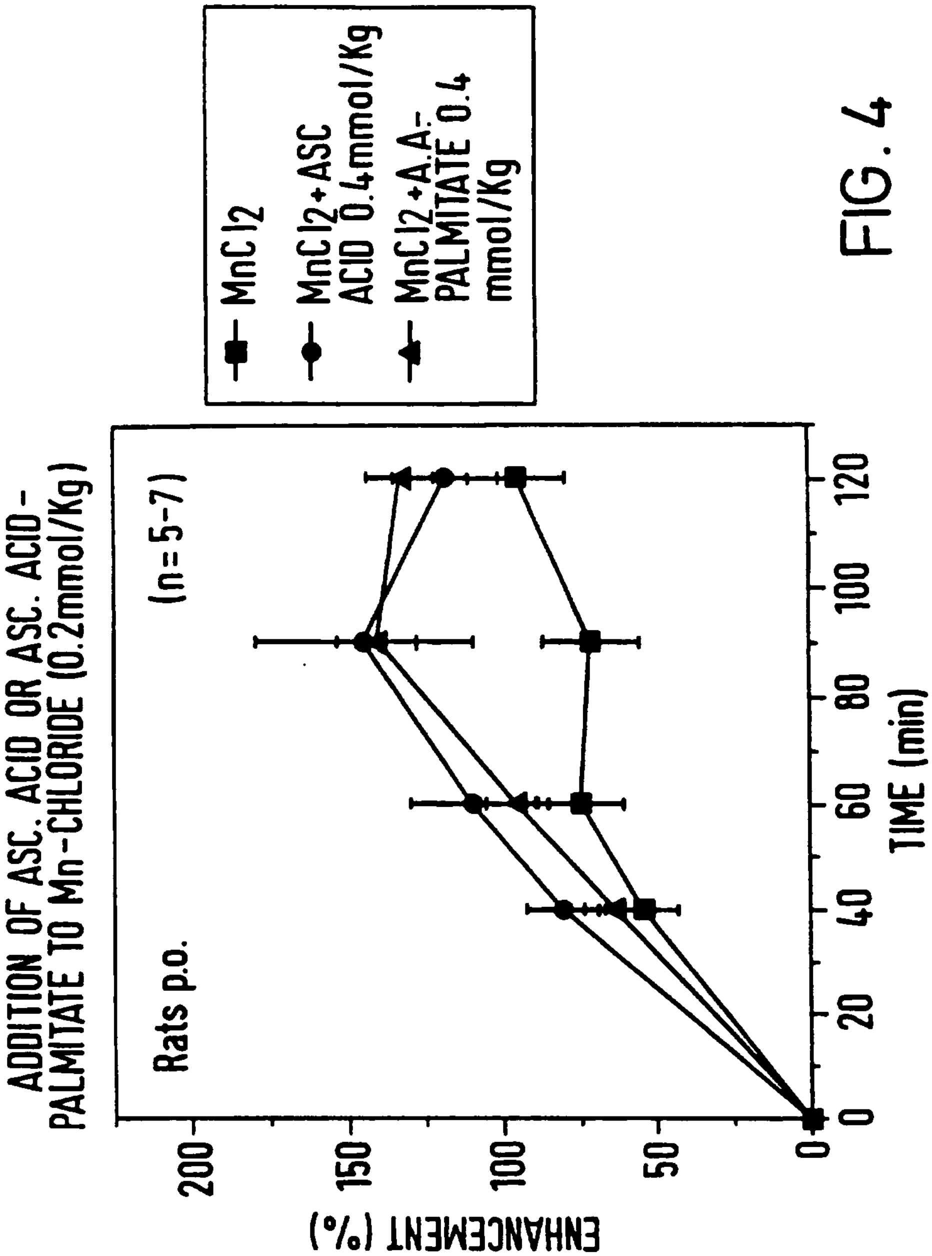

ADDITION OF ASC. ACID OR ASC. ACID-PALMITATE TO Mn-CHLORIDE (0.2mmol/Kg)
Rats p.o.
(n=5-7)
MnCl2
MnCl2+ASC ACID 0.4mmol/Kg
MnCl2+A.A.-PALMITATE 0.4 mmol/Kg
ENHANCEMENT (%)
0
50
100
150
200
TIME (min)
0
20
40
60
80
100
120

FIG. 4

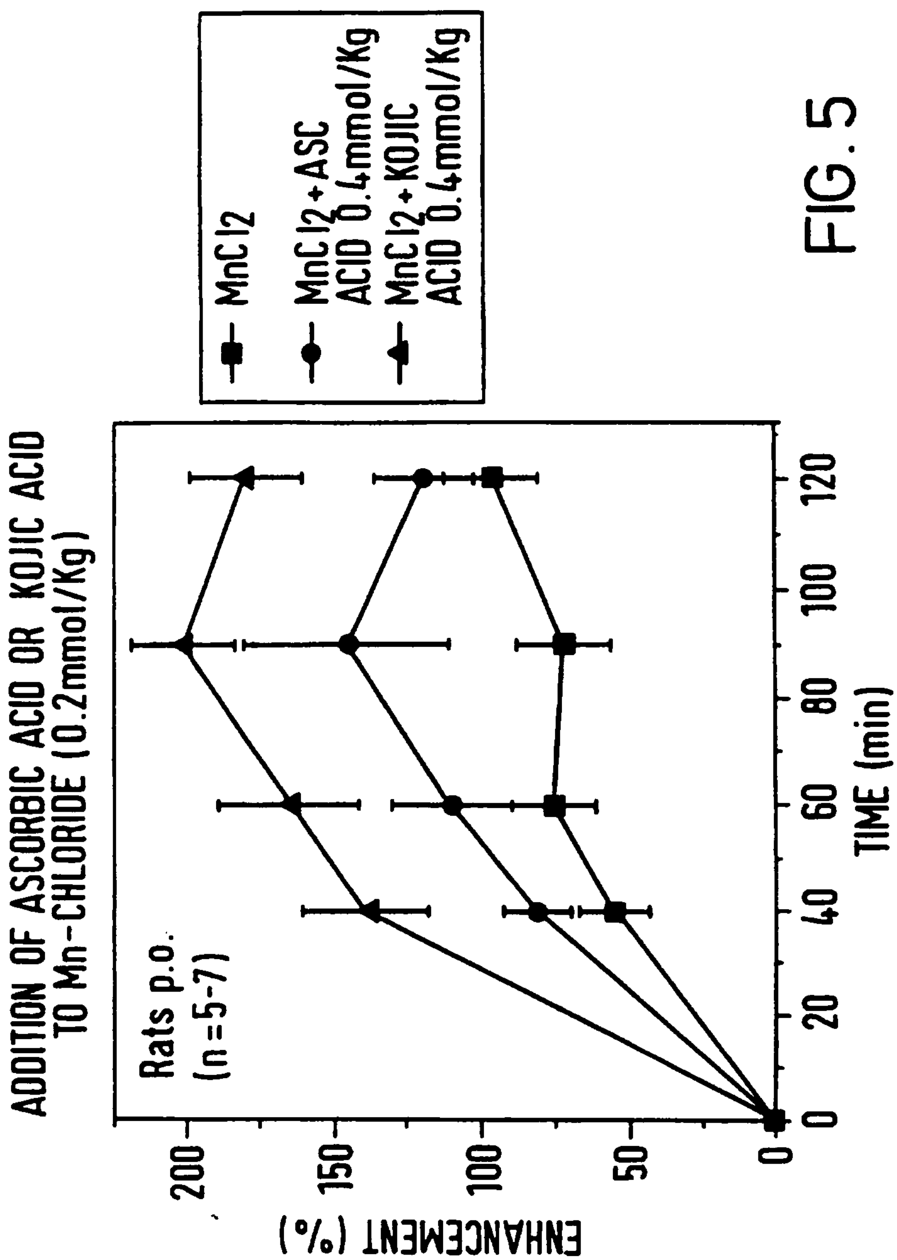

ADDITION OF ASCORBIC ACID OR KOJIC ACID
TO Mn-CHLORIDE (0.2mmol/Kg)
Rats p.o.
(n=5-7)
ENHANCEMENT (%)
TIME (min)
0
50
100
150
200
0
20
40
60
80
100
120
MnCl2
MnCl2+ASC ACID 0.4mmol/Kg
MnCl2+KOJIC ACID 0.4mmol/Kg

FIG. 5

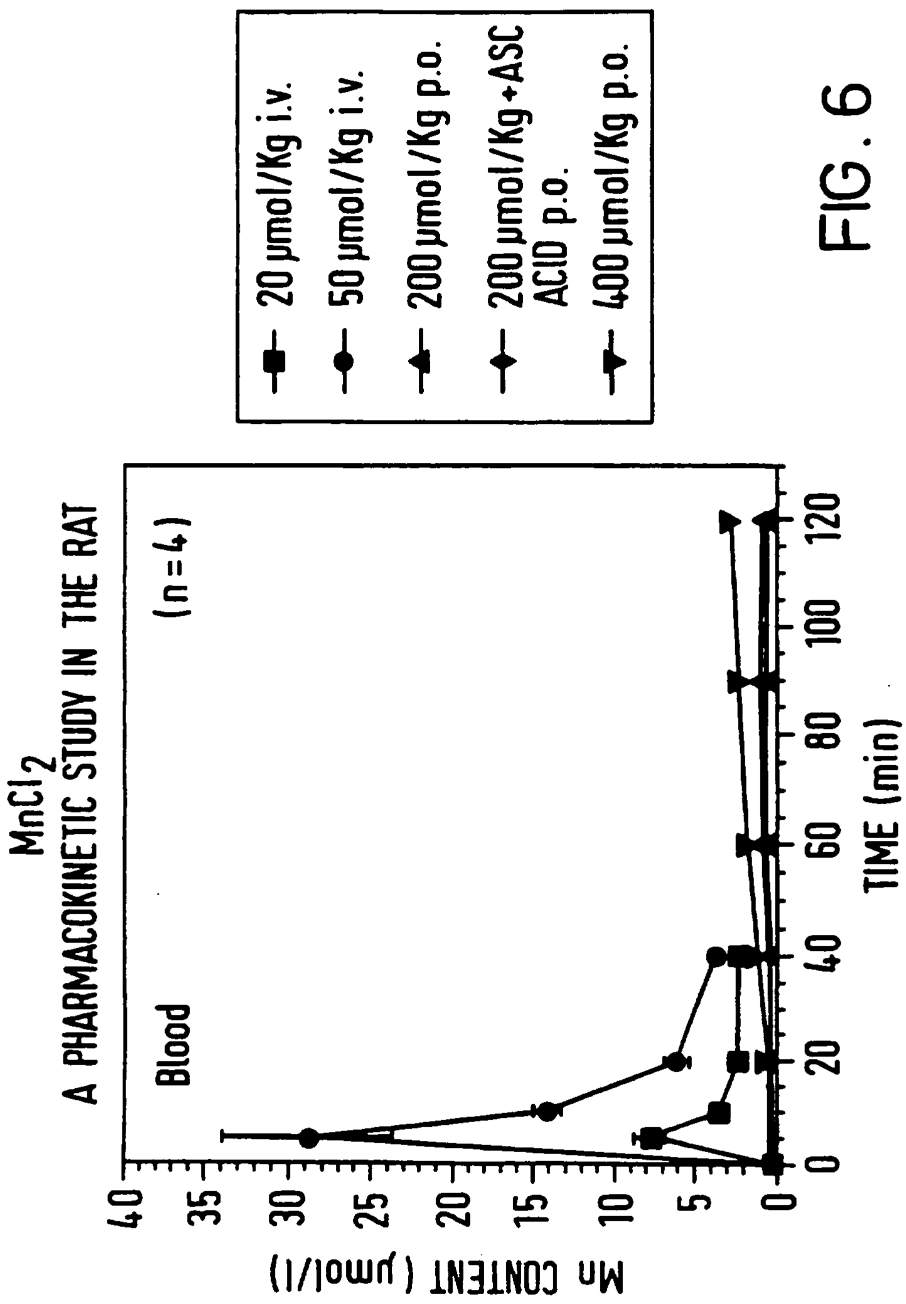

MnCl2
A PHARMACOKINETIC STUDY IN THE RAT
Blood
(n=4)
Mn CONTENT (µmol/l)
0
5
10
15
20
25
30
35
40
0
20
40
60
80
100
120
TIME (min)
20 µmol/Kg i.v.
50 µmol/Kg i.v.
200 µmol/Kg p.o.
200 µmol/Kg+ASC ACID p.o.
400 µmol/Kg p.o.

FIG. 6

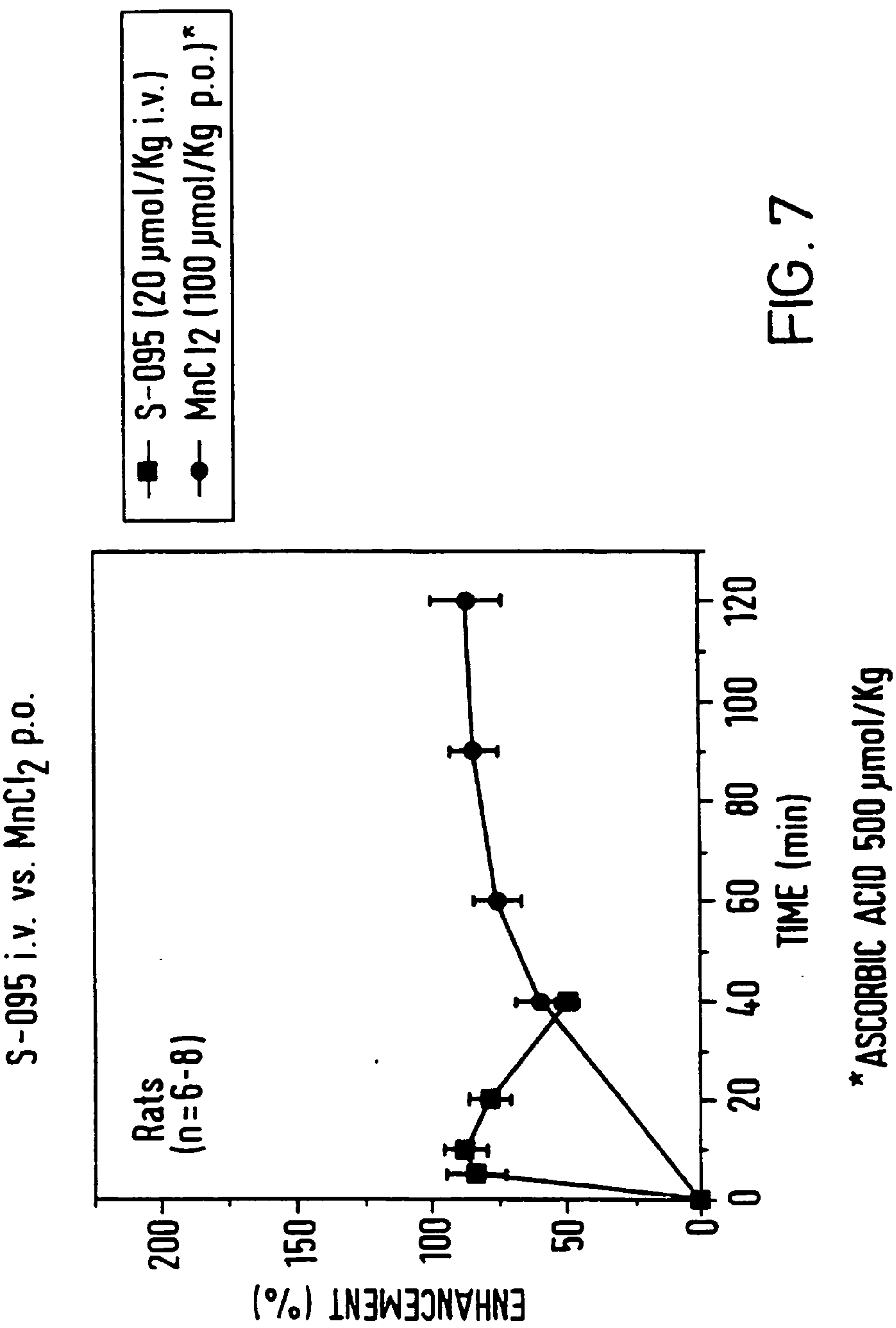

S-095 i.v. vs. MnCl2 p.o.
S-095 (20 µmol/Kg i.v.)
MnCl2 (100 µmol/Kg p.o.)*
Rats
(n=6-8)
ENHANCEMENT (%)
200
150
100
50
0
0
20
40
60
80
100
120
TIME (min)
*ASCORBIC ACID 500 µmol/Kg

FIG. 7

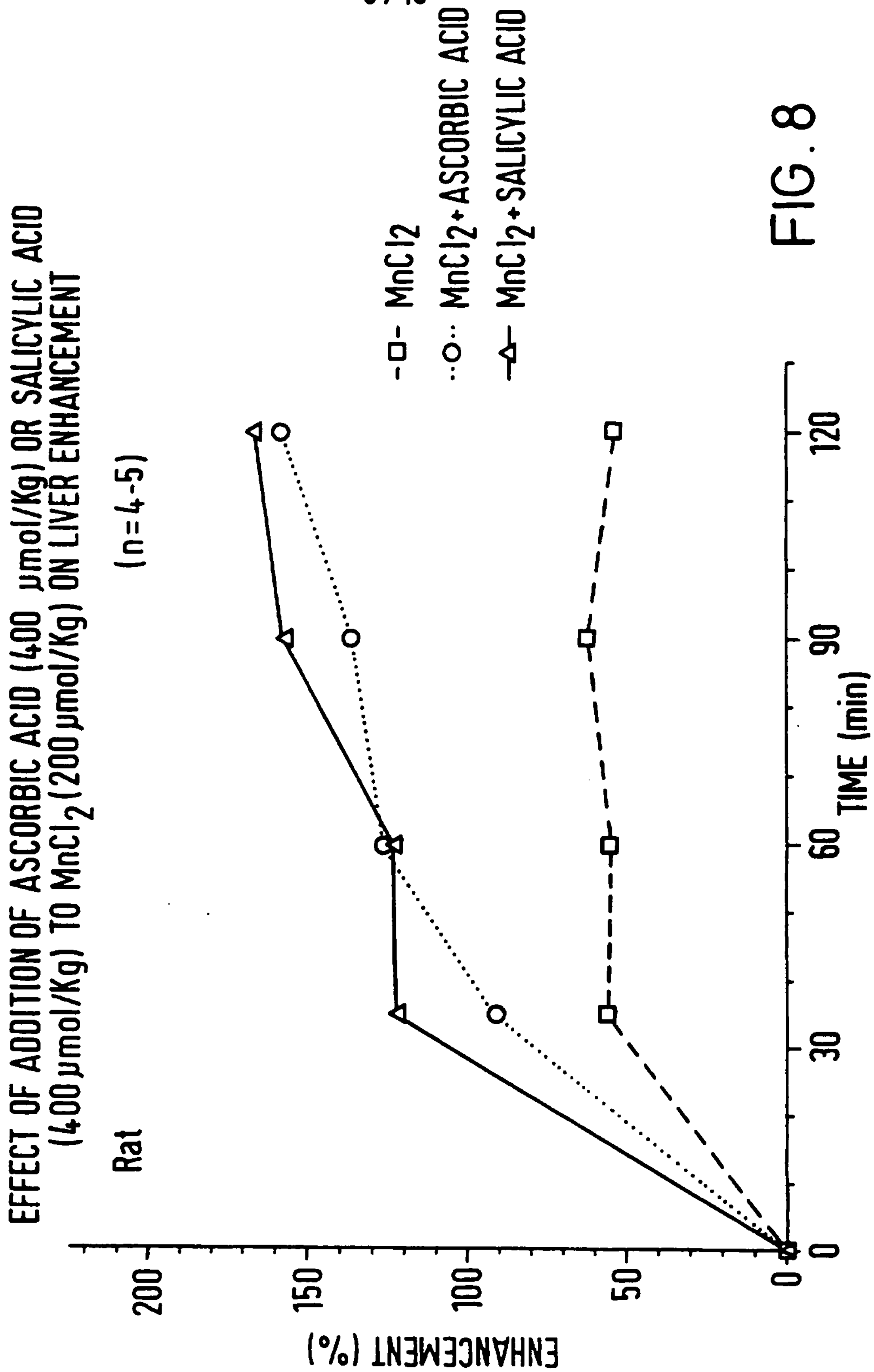

EFFECT OF ADDITION OF ASCORBIC ACID (400 μmol/Kg) OR SALICYLIC ACID
(400 μmol/Kg) TO MnCl2 (200 μmol/Kg) ON LIVER ENHANCEMENT
(n=4-5)
Rat
-□- MnCl2
··○·· MnCl2+ASCORBIC ACID
—△— MnCl2+SALICYLIC ACID
ENHANCEMENT (%)
200
150
100
50
0
0
30
60
90
120
TIME (min)

FIG. 8

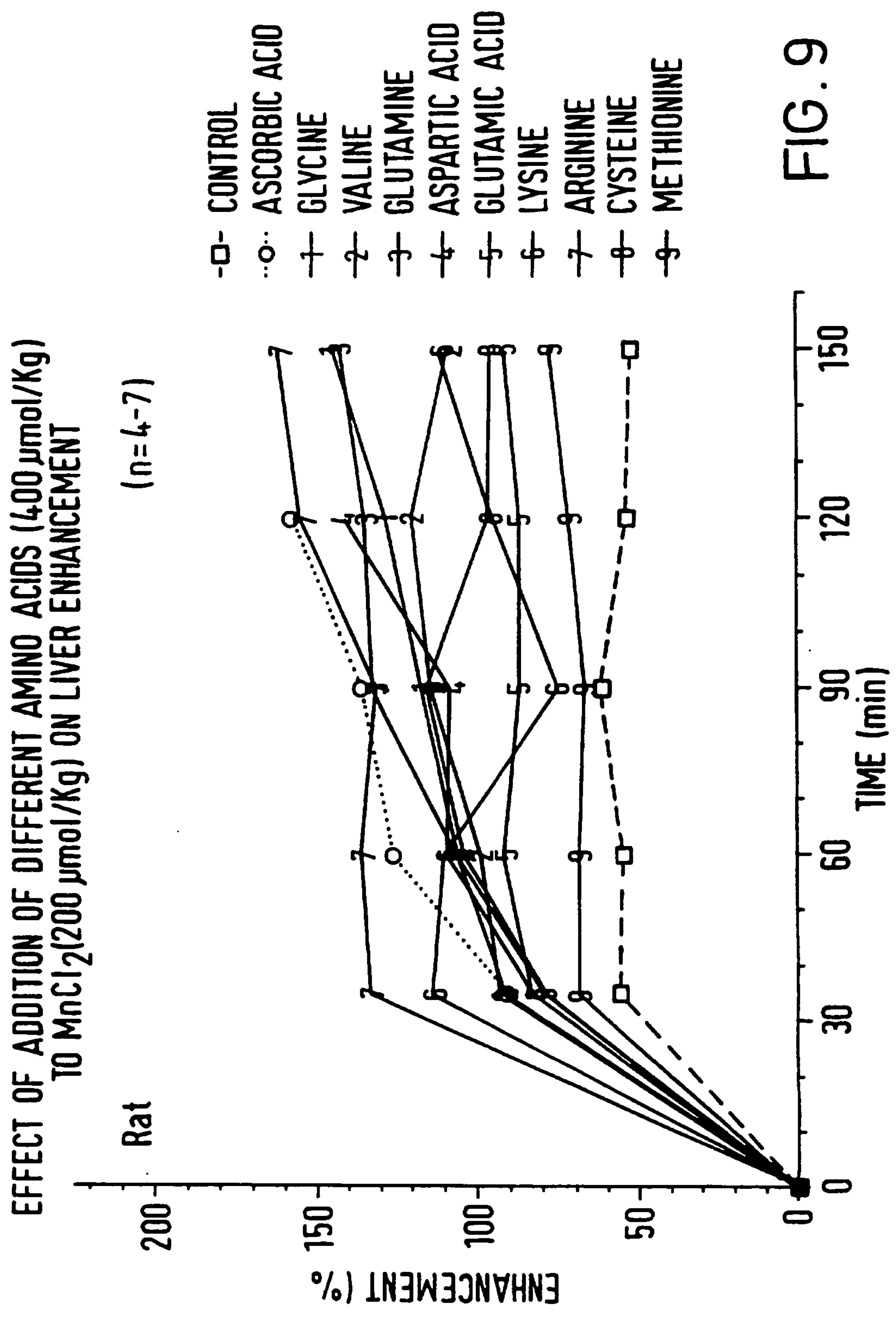

EFFECT OF ADDITION OF DIFFERENT AMINO ACIDS (400 µmol/Kg) TO MnCl2(200 µmol/Kg) ON LIVER ENHANCEMENT
Rat
(n=4-7)
ENHANCEMENT (%)
0
50
100
150
200
TIME (min)
0
30
60
90
120
150
CONTROL
ASCORBIC ACID
GLYCINE
VALINE
GLUTAMINE
ASPARTIC ACID
GLUTAMIC ACID
LYSINE
ARGININE
CYSTEINE
METHIONINE

FIG. 9

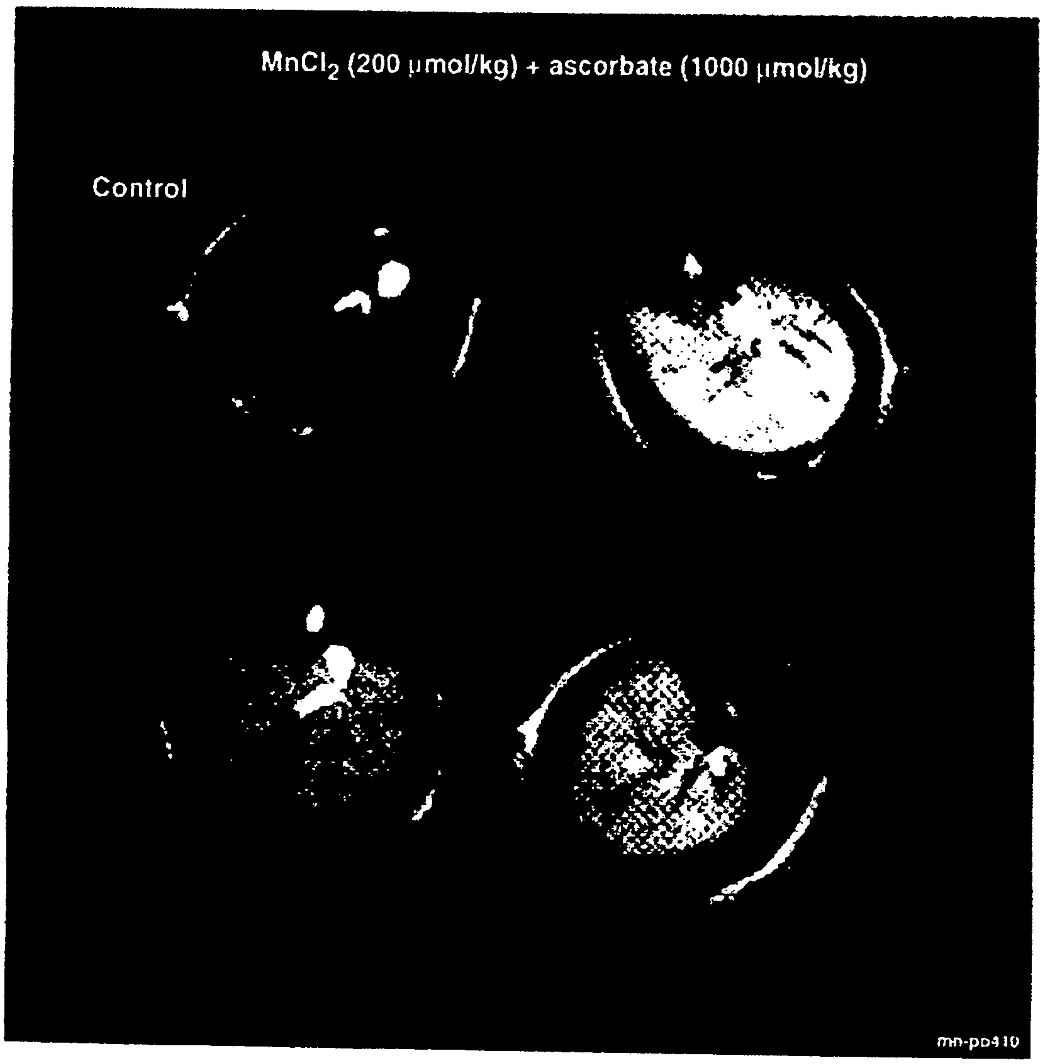


FIG.10

FIG.11

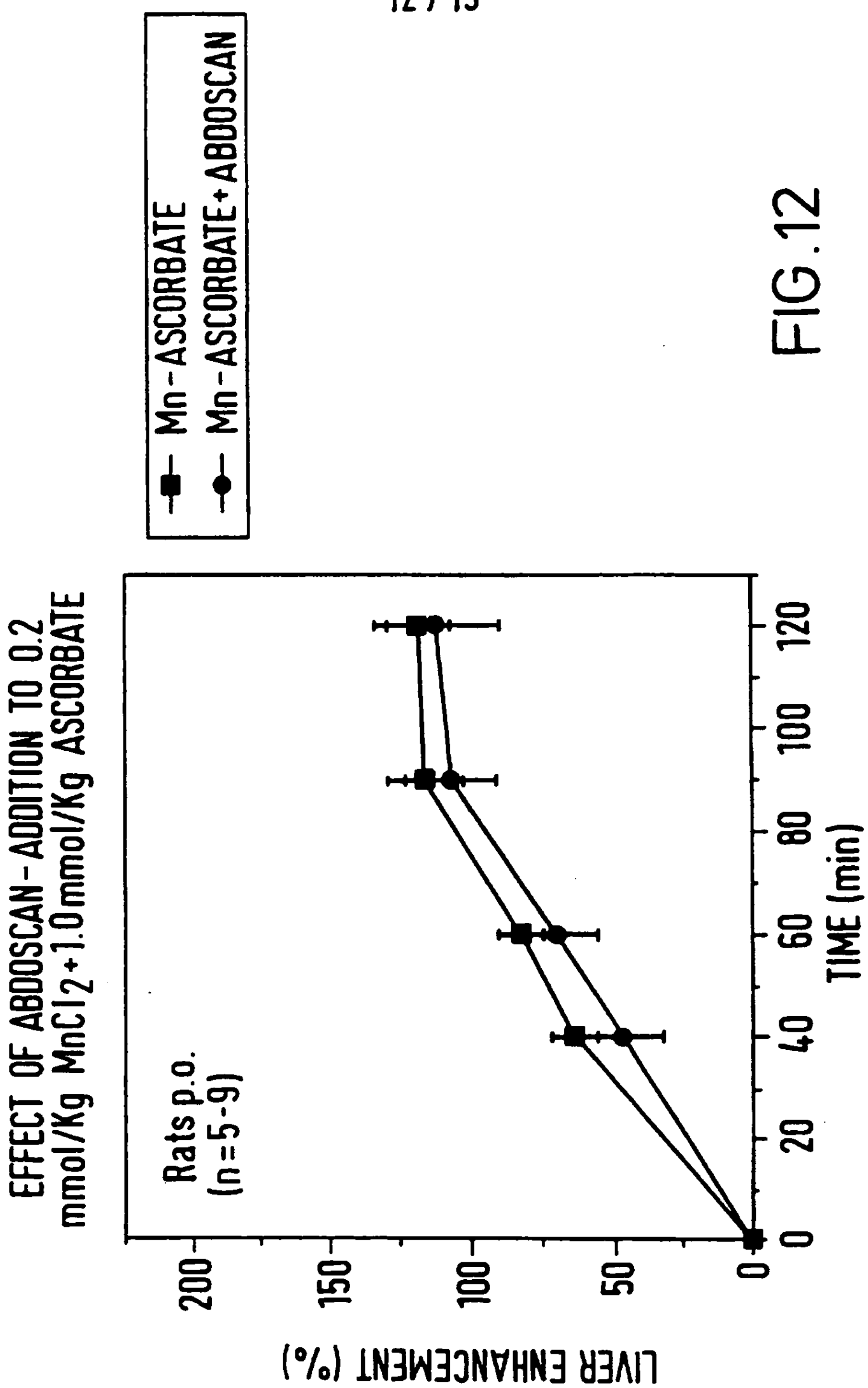

EFFECT OF ABDOSCAN-ADDITION TO 0.2 mmol/Kg MnCl2+1.0mmol/Kg ASCORBATE
Mn-ASCORBATE
Mn-ASCORBATE+ABDOSCAN
Rats p.o.
(n=5-9)
LIVER ENHANCEMENT (%)
TIME (min)
0
50
100
150
200
0
20
40
60
80
100
120

FIG.12

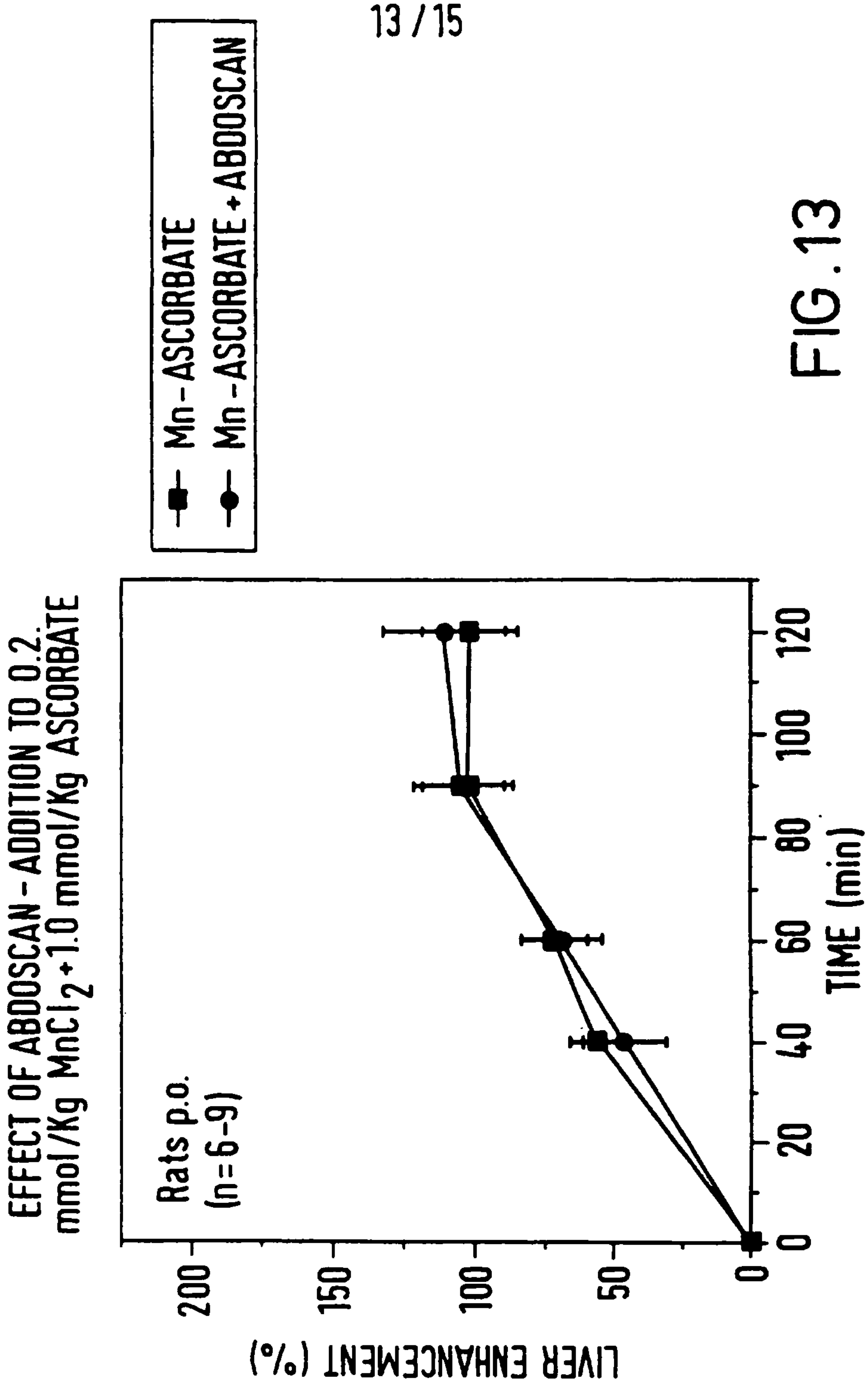

EFFECT OF ABDOSCAN - ADDITION TO 0.2. mmol/Kg $MnCl_2$+1.0 mmol/Kg ASCORBATE
Mn - ASCORBATE
Mn - ASCORBATE + ABDOSCAN
Rats p.o.
(n=6-9)
LIVER ENHANCEMENT (%)
0
50
100
150
200
TIME (min)
0
20
40
60
80
100
120

FIG. 13

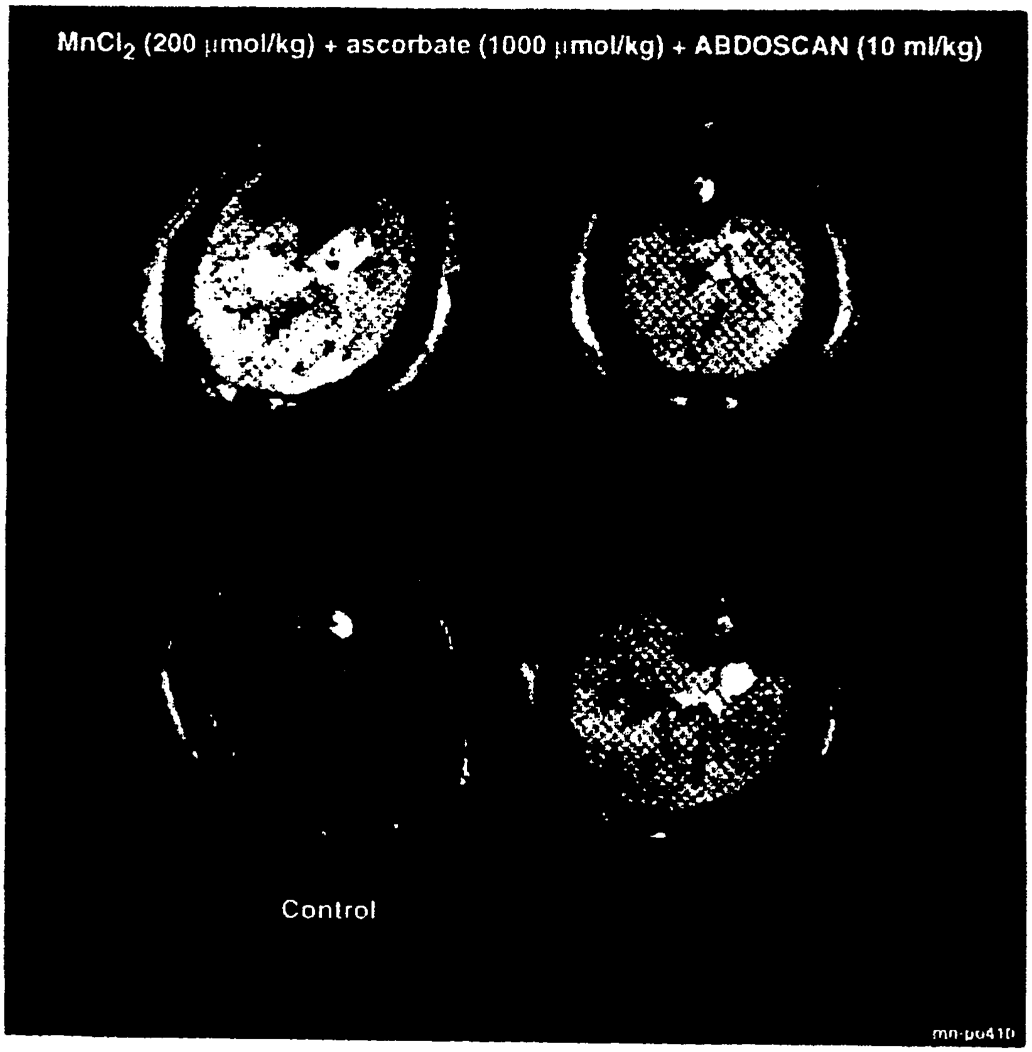

MnCl2 (200 μmol/kg) + ascorbate (1000 μmol/kg) + ABDOSCAN (10 ml/kg)
Control
mn-po410

FIG. 14

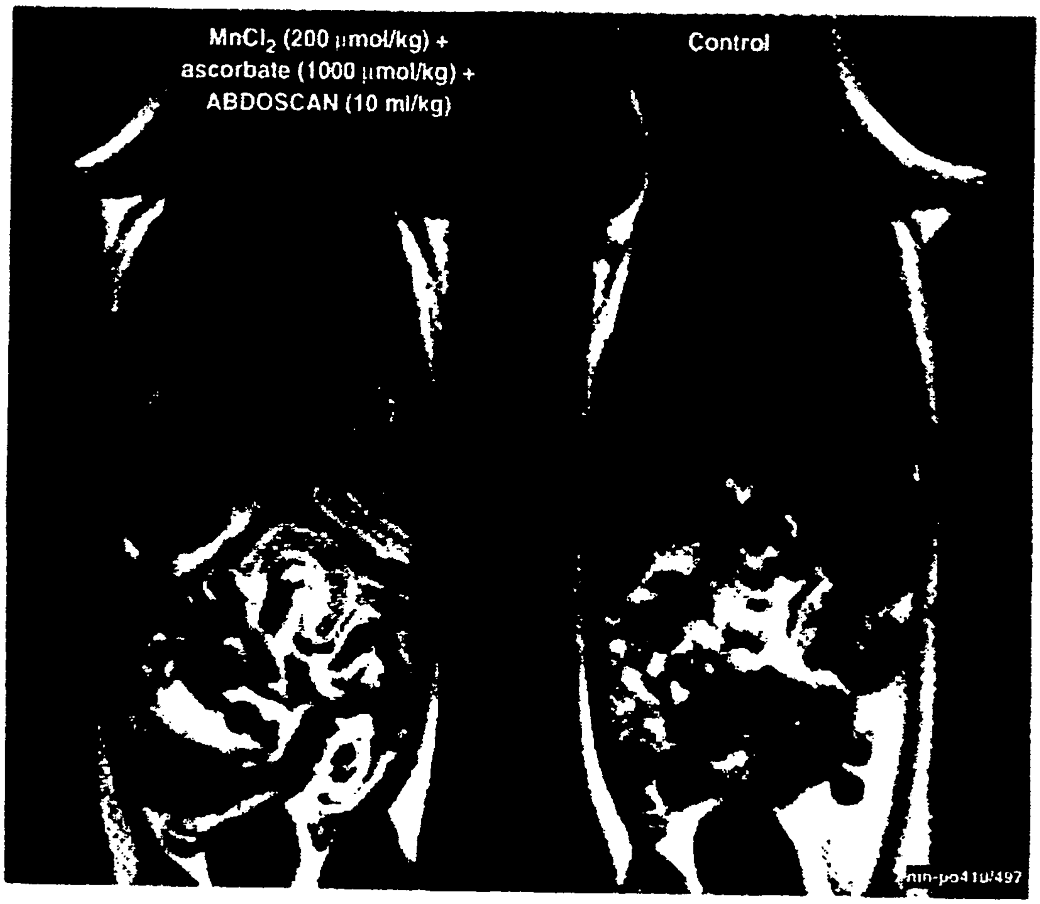

$MnCl_2$ (200 µmol/kg) +
ascorbate (1000 µmol/kg) +
ABDOSCAN (10 ml/kg)
Control

FIG.15

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9416768.1	18 August 1994 (18.08.94)	GB

(60) Parent Applications or Grants

(63) Related by Continuation

US	08/462,873 (CIP)
Filed on	5 June 1995 (05.06.95)
US	08/465,100 (CIP)
Filed on	5 June 1995 (05.06.95)

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(71) Applicant (*for GB only*): COCKBAIN, Julian [GB/GB]; 27 Ladbroke Road, London W11 3PD (GB).

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(75) Inventors/Applicants (*for US only*): GOLMAN, Klaes [DK/DK]; Rungstedvej 85, DK-2960 Rungsted Kyst (DK). PETTERSSON, Göran [SE/SE]; Mårtens Väg 5, S-245 63 Hjärup (SE). BERG, Arne [NO/NO]; Stasjonsveien 37D, N-1310 Blommenholm (NO). KLAVENESS, Jo [NO/NO]; Midtåsen 5B, N-1166 Oslo (NO). RONGVED, Pål [NO/NO]; Hondensvei 11, N-1450 Nesoddtangen (NO). LEANDER, Peter [SE/SE]; Möllevångsgatan 31, S-222 40 Lund (SE). LEUNBACH, Ib [DK/DK]; St. Magleby Strandvej 5, DK-2791 Dragör (DK). GUNTHER, Wolfgang [US/US]; 606 John Anthony Drive, West Chester, PA 19382 (US).

(74) Agents: COCKBAIN, Julian et al.; Frank B. Dehn & Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published

With international search report.

(88) Date of publication of the international search report: 11 July 1996 (11.07.96)

(54) Title: COMPOSITIONS

(57) Abstract

There is provided a contrast medium composition comprising a physiologically tolerable manganese compound, an uptake promoter and a physiologically tolerable carrier or excipient, having a manganese concentration of at least 0.3mM or being in a dosage unit form containing at least 300 μmol manganese, wherein the uptake promoter comprises a physiologically tolerable reducing compound containing an α-hydroxy ketone group, a physiologically tolerable acid containing α- and/or β-hydroxy or amino groups, or a salt thereof, and/or vitamin D. Such compositions are particularly suitable for imaging of the liver.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 95/01969

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K49/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PROC. SOC. EXP. BIOL. MED., VOL. 199, NO. 4, PAGE(S) 470-80, 1992 JOHNSON, PHYLLIS E. ET AL 'Effects of copper, iron, and ascorbic acid on managanese availability to rats' see abstract see page 473, left column see table 2 see Discussion ---	1-5, 12-15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

3

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 1996	29.04.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Dullaart, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BIOL. TRACE ELEM. RES., VOL. 41, NO. 3, PAGE(S) 279-94, June 1994 SEABORN, CAROL D. ET AL 'Chromium and chronic ascorbic acid depletion effects on tissue ascorbate, manganese, and 14C retention from 14C-ascorbate in guinea pigs' see abstract see table 6 see page 293 ---	1-5, 12-15
X	J. TOXICOL. ENVIRON. HEALTH, VOL. 26, NO. 4, PAGE(S) 387-98, 1989 BELL, JANET G. ET AL 'Higher retention of manganese in suckling than in adult rats is not due to maturational differences in manganese uptake by rat small intestine' see abstract see figure 4 see page 396 ---	1-5, 12-15
X	WO,A,87 04622 (ALBION LAB) 13 August 1987 see examples 13,14,28 ---	1-5, 12-15
X	US,A,5 292 729 (ASHMEAD HARVEY H) 8 March 1994 see abstract see example 12 see claims ---	1-5, 12-15
X	EP,A,0 524 633 (BERES EXPORT IMPORT RT) 27 January 1993 see complex V see examples 1-4 see claims 1,7,27,34,36 ---	1-5, 12-15
A	STUD. CERCET. BIOL., SER. BIOL. ANIM., VOL. 44, NO. 2, PAGE(S) 135-7, 1992 GIURGEA, RODICA ET AL 'Effects of acute manganese treatment on biochemical parameters in chickens' see abstract see table 1 ---	1-5, 12-15

-/--

3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 95/01969

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	J NUTR, DEC 1989, VOL. 119, NO. 12 SUPPL, PAGE(S) 1839-44;DISCUSSION 1845, LONNERDAL B 'Trace element absorption in infants as a foundation to setting upper limits for trace elements in infant formulas.' see abstract see page 1842, right column - page 1843 ---	1-5, 12-15
Y	BULL. SOC. CHIM. FR., 1975,, NO. 11-12, PT. 1, PAGE(S) 2404-8, GERARD C ET AL 'Thermodynamic stability of complexes of kojic acid an.alpha.-keto enol, with divalent cations: manganese, cobalt, nickel, copper and zinc' see abstract see figures see tables ---	1-4,6, 12-15
Y	BULL. SOC. CHIM. FR., no. 11-12, 1979 pages 451-456, GERARD, CHRISTIAN 'Studies of neutral complexes of kojic acid and maltol with divalent manganese, cobalt, nickel, copper, and zinc cations' see abstract see tables 1,5 ---	1-4,6, 12-15
Y	EP,A,0 401 096 (LABORATOIRES LUCIEN ET AL.) 5 December 1990 see abstract see examples see claims ---	1-4,6, 12-15
Y	WO,A,93 06811 (THE UNIVERSITY OF BRITISH COLUMBIA) 15 April 1993 see abstract see examples 2,5 see table 3 see claims ---	1-4,6, 12-15
X	MAGN. RESON. MED., 1992, VOL. 23, NO. 1, PAGE(S) 154-165, XP 000250035 RUBIN D.L. ET AL 'Formulation of radiographically detectable gastrointestinal contrast agents for magnetic resonance imaging: Effects of a barium sulfate additive on MR contrast agent effectiveness' see abstract see tables see figures see page 164 --- -/--	16-21,23

3

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. COORD. CHEM., 1972, VOL. 1, NO. 3, PAGE(S) 173-7, XP 000565612 STAMPFLI R ET AL 'Thermodynamics of Kojate complexes of the lanthanides' see abstract see tables 1-4 see figures 1-3 ---	16-21,23
Y	FINN. CHEM. LETT., 1986, VOL. 13, NO. 5, PAGE(S) 129-35, XP 000565614 PETROLA R 'Stability of yttrium(III) complexes of substituted 3-hydroxy-4H-pyran-4-ones in aqueous solution' see abstract see tables 1,4 -----	16-21,23

3

International application No.
PCT/GB95/01969

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 14, 22 are directed to a treatment/diagnosis of th
e human/animal body, the seach has been carried out, based on the alleged e
ffects of the compound/composition (Rule 39.1(iv) PCT).

2. [X] Claims Nos.: 1-4,12-23
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
In view of the large number of compounds, which are defined by the general definitions of the compounds used in claim(s) 1-4, 12-15 and 16-23, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and / or the compounds mentioned in the claims, and to the general idea underlying the application (see Guidelines, chapter III, paragraph 2.3).

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Six different inventions were stated. For further information please see continuation sheet!

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
Claim groups 1, 2
and 6

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

PCT/GB95/01969

1 YES Claim 5, and part of claims 1-4 and 12-15: a contrast medium composition, in which the contrast agent is containing a manganese salt, and the uptake promoter ascorbic acid, its use in magnetic resonance imaging, and a kit for preparing the contrast medium composition.

2 YES Claim 6, and part of claims 1-4 and 12-15: a contrast medium composition, in which the contrast agent is containing a manganese salt, and the uptake promoter kojic acid, its use in magnetic resonance imaging, and a kit for preparing the contrast medium composition.

3 NO Claim 7, and part of claims 1-3 and 12-15: a contrast medium composition, in which the contrast agent is containing a manganese salt, and as uptake promoter gluconic or salicylic acid, its use in magnetic resonance imaging, and a kit for preparing the contrast medium composition.

4 NO Claims 8-10, and part of claims 1-3 and 12-15: a contrast medium composition, in which the contrast agent is containing a manganese salt, and as uptake promoter an α- or β-amino acid, its use in magnetic resonance imaging, and a kit for preparing the contrast medium composition.

5 NO Claim 11, and part of claims 1-3 and 12-15: a contrast medium composition, in which the contrast agent is containing a manganese salt, and as uptake promoter vitamin D, its use in magnetic resonance imaging, and a kit for preparing the contrast medium composition.

6 YES Claims 16-23: a contrast medium composition containing a manganese salt, an uptake promoter, together with a second contrast agent, its use in magnetic resonance imaging, and a kit for preparing the contrast medium composition.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

The problem underlying the present application is, in its broadest from, the provision of safer contrast agents for NMR imaging, containing manganese ions.

As solution to this problem, different uptake promoters are used.

The special technical feature, linking these solutions together, is the use of an uptake promotor for manganese ions.

This use is already known in the prior art. **Biol. Trace Elem. Res., 1994, Vol. 41, No. 3, page(s) 279-94** demonstrates, that both the uptake and the distribution of Mn are affected by dietary ascorbate. Although in **Proc. Soc. Exp. Biol. Med., 1992, Vol. 199, No. 4, page(s) 470-80**, ascorbate is said not to influence the liver uptake of Mn, it also shows an increased liver/plasma ratio of Mn with increased ascorbate intake (see page 476, left hand column; table II and discussion).

Moreover, several compositions containing both a manganese salt and one of the uptake promoters mentioned, have been described before: see e.g. **EP-A-524 633** (complex V; examples 1-4; claims 1, 7, 27, 34 and 36), **US-A-5 292 729** (see *inter alia* example 12) and **WO-A-87/04622** (see examples 13, 14 and 28). In the latter document, the complexes are used for delivery to specific biological tissue sites.

For this reason, the special technical feature mentioned above can no longer be accepted as technical feature linking the different inventions together. Therefore, the present application lacks unity of invention, containing the following subjects.

Since searching this plurality of different subjects would have caused major additional searching efforts, initially, a search was performed for the first subject only.
After payment of 2 (two) further search fees, a search was performed for subjects Nos. 2 and 6.

INTERNATIONAL SEARCH REPORT

Inte   onal Application No
PCT/GB 95/01969

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